Reducing Radiobiological Uncertainty in Proton Therapy Treatment Planning

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Talk Outline

- Overview of proton therapy and its associated uncertainties
- Radiobiological uncertainty and how we quantify/model it
- Can the modelling be improved?
- How can be apply this to a treatment plan?

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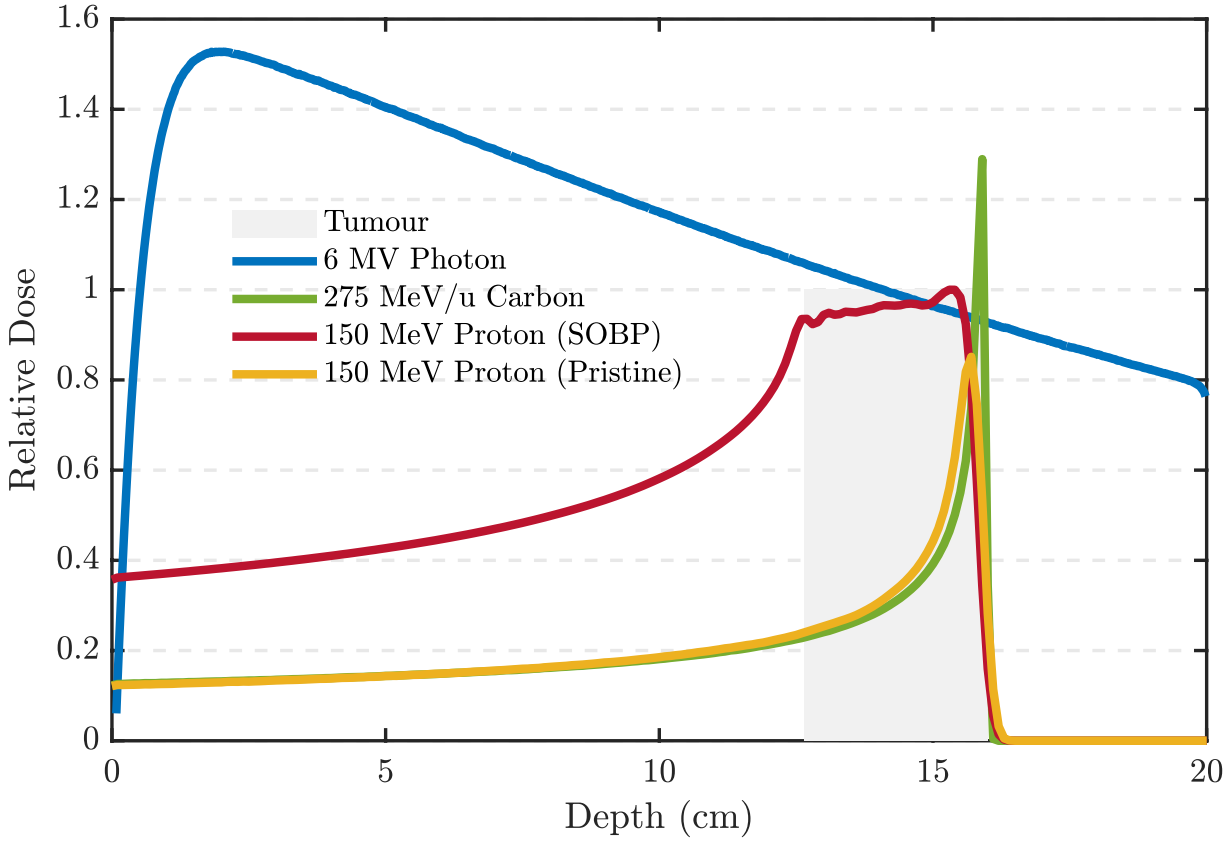
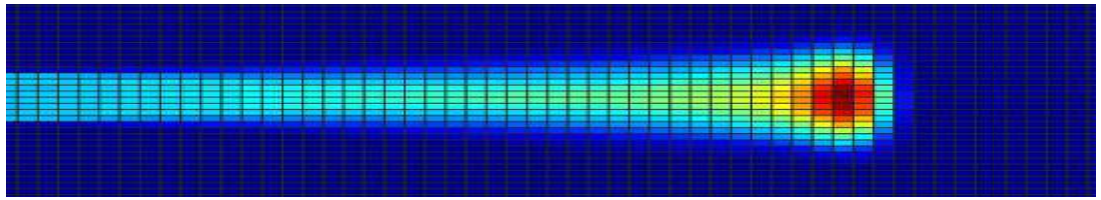
What is proton therapy?





- Proton therapy is a type of cancer treatment delivered via an external beam
- Protons/heavy ions allow high tumour dose, lower integral build-up dose and zero exit dose via the Bragg Peak
- The Bragg Peak can be modulated to match the tumour width. We call this the spread-out Bragg Peak (SOBP)
- Whereas conventional radiotherapy delivered by photons which deliver a higher integral dose to organs at risk

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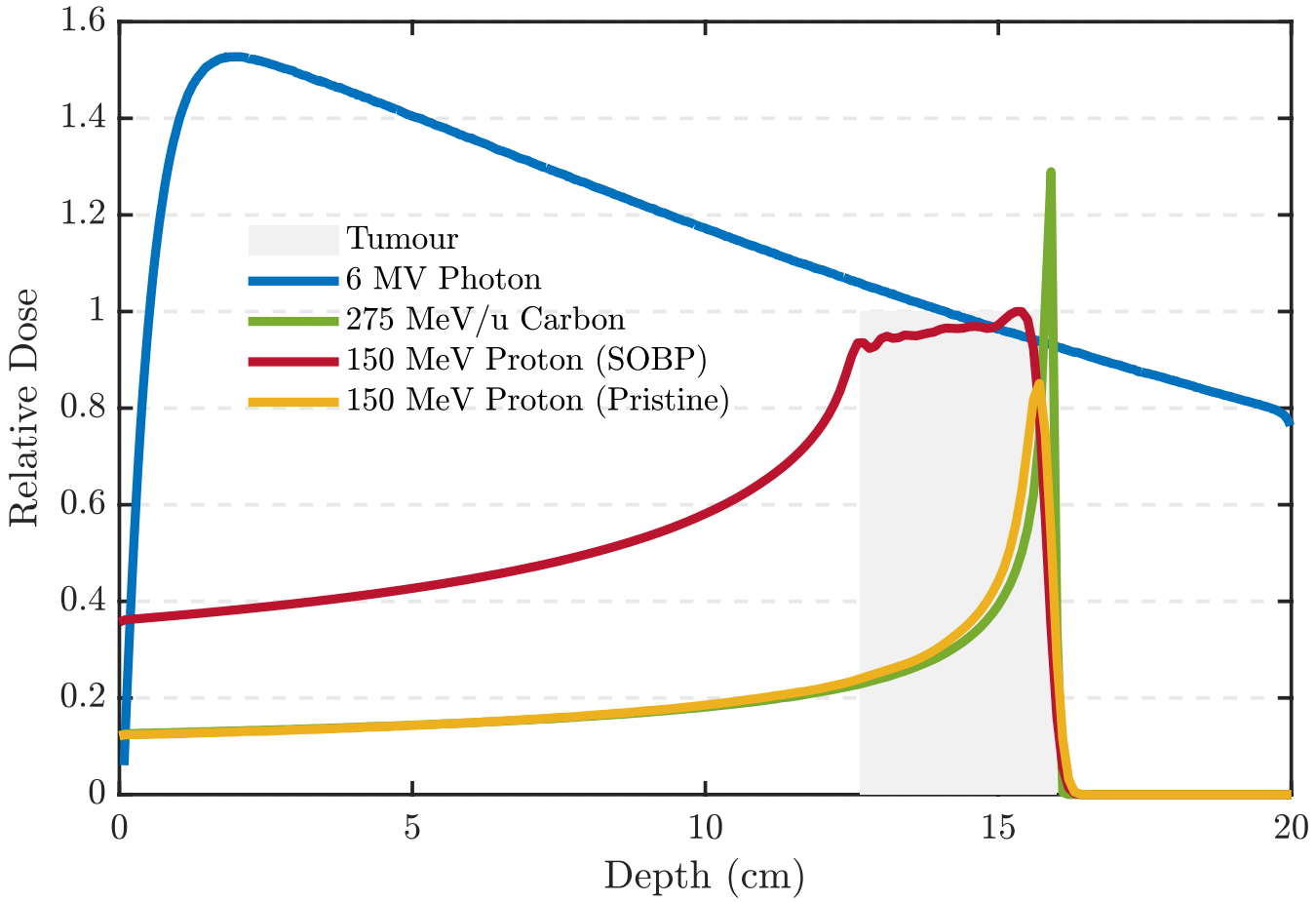
Uncertainties in Proton Therapy



- Range Uncertainties
  - Discrepancies in stopping powers

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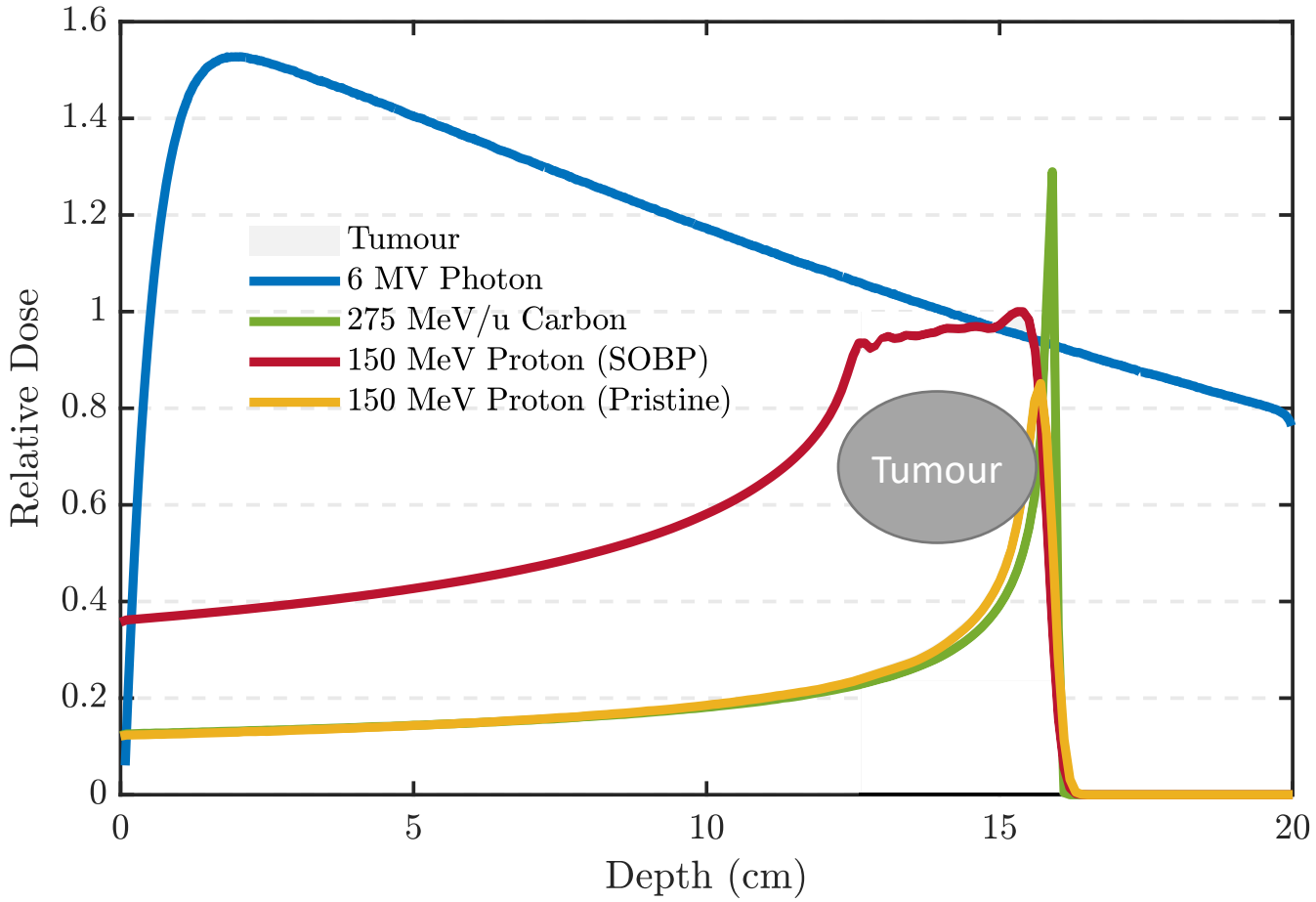
Uncertainties in Proton Therapy



- Range Uncertainties
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  - Patient breathing during treatments
  - Patient shifting between/during treatment
  - Organ filling/emptying

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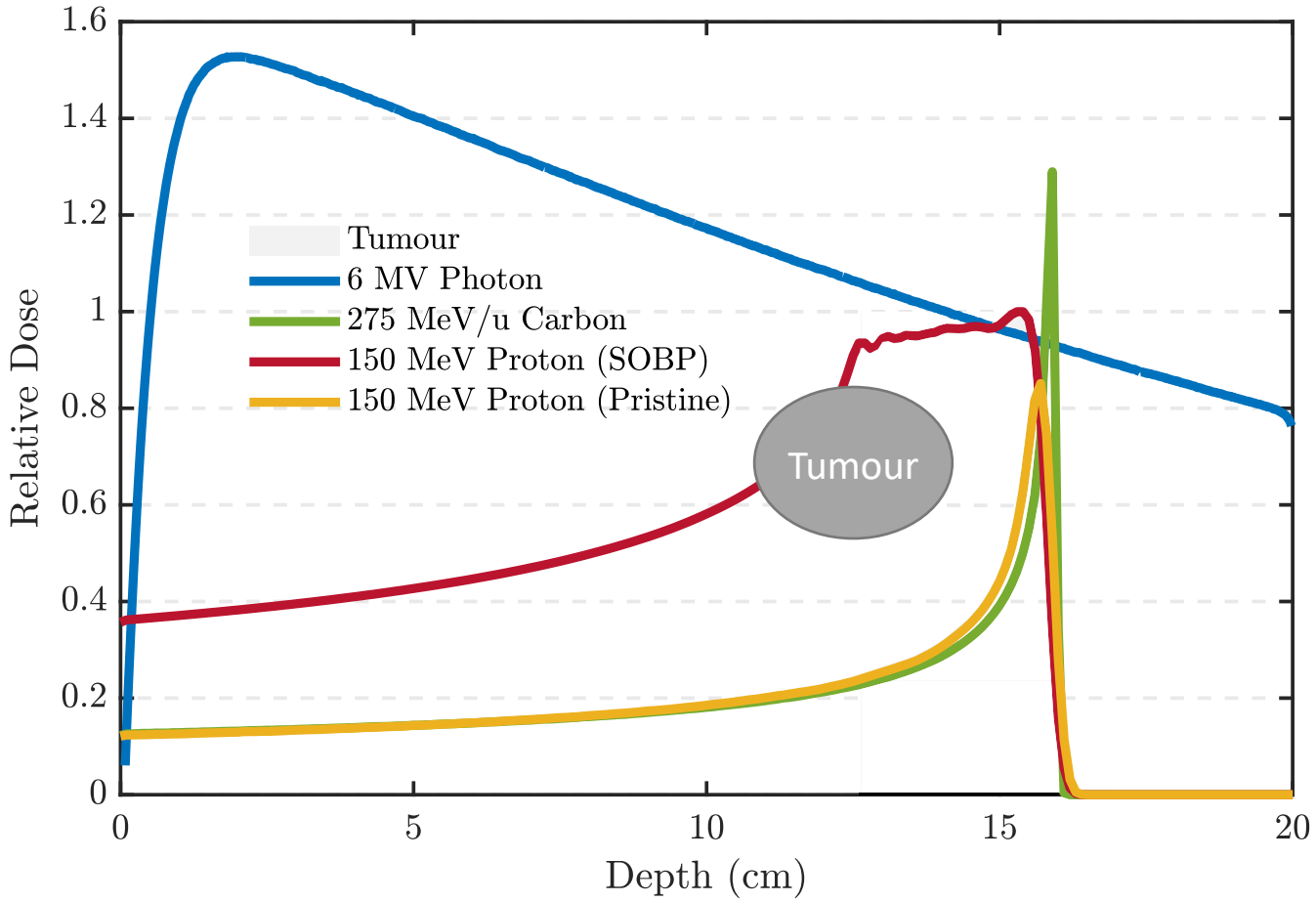
Uncertainties in Proton Therapy



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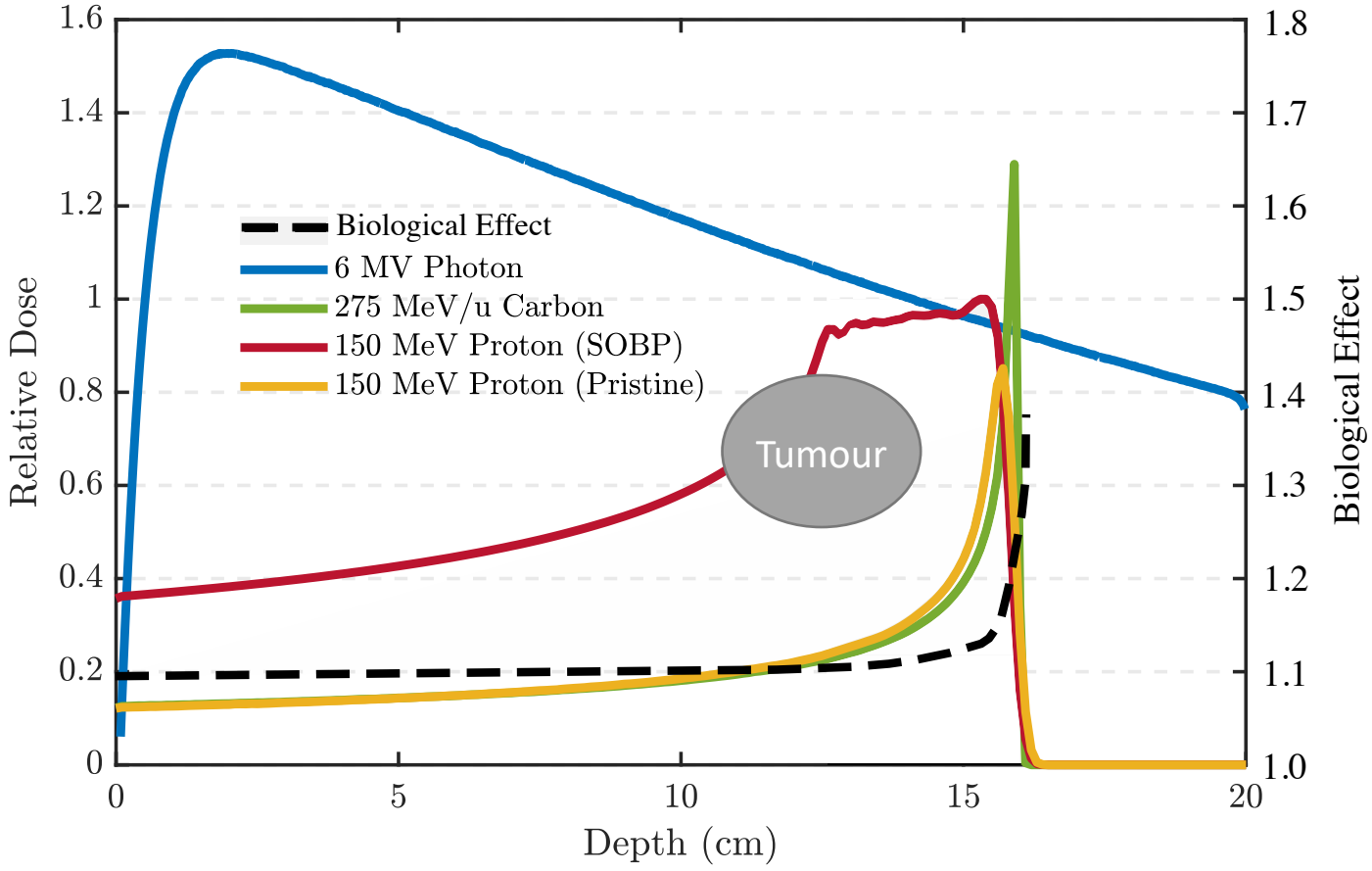

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- Radiobiological Uncertainties
  - Protons are more biologically effective in the “fall-off” region of the Bragg Peak

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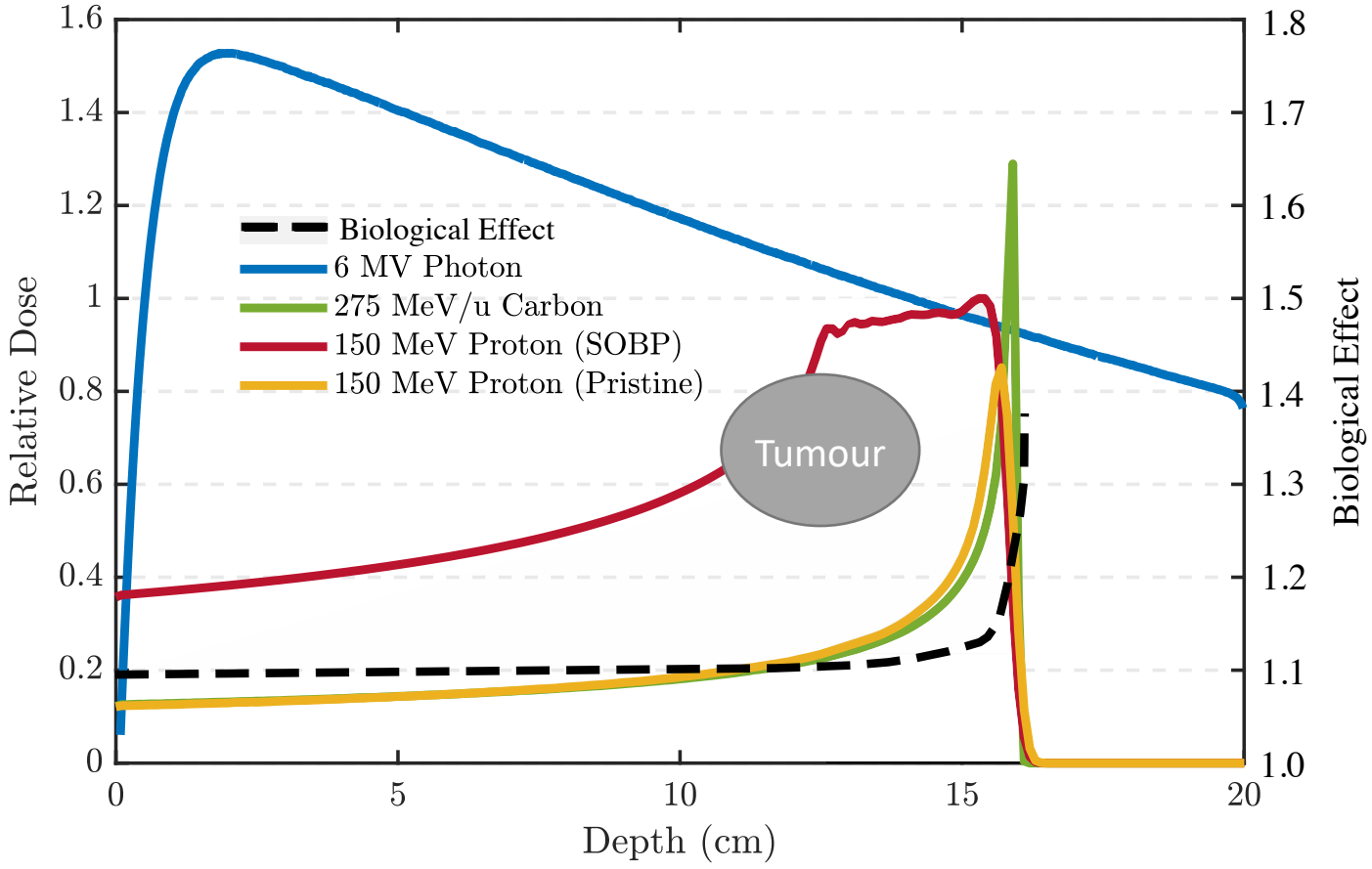

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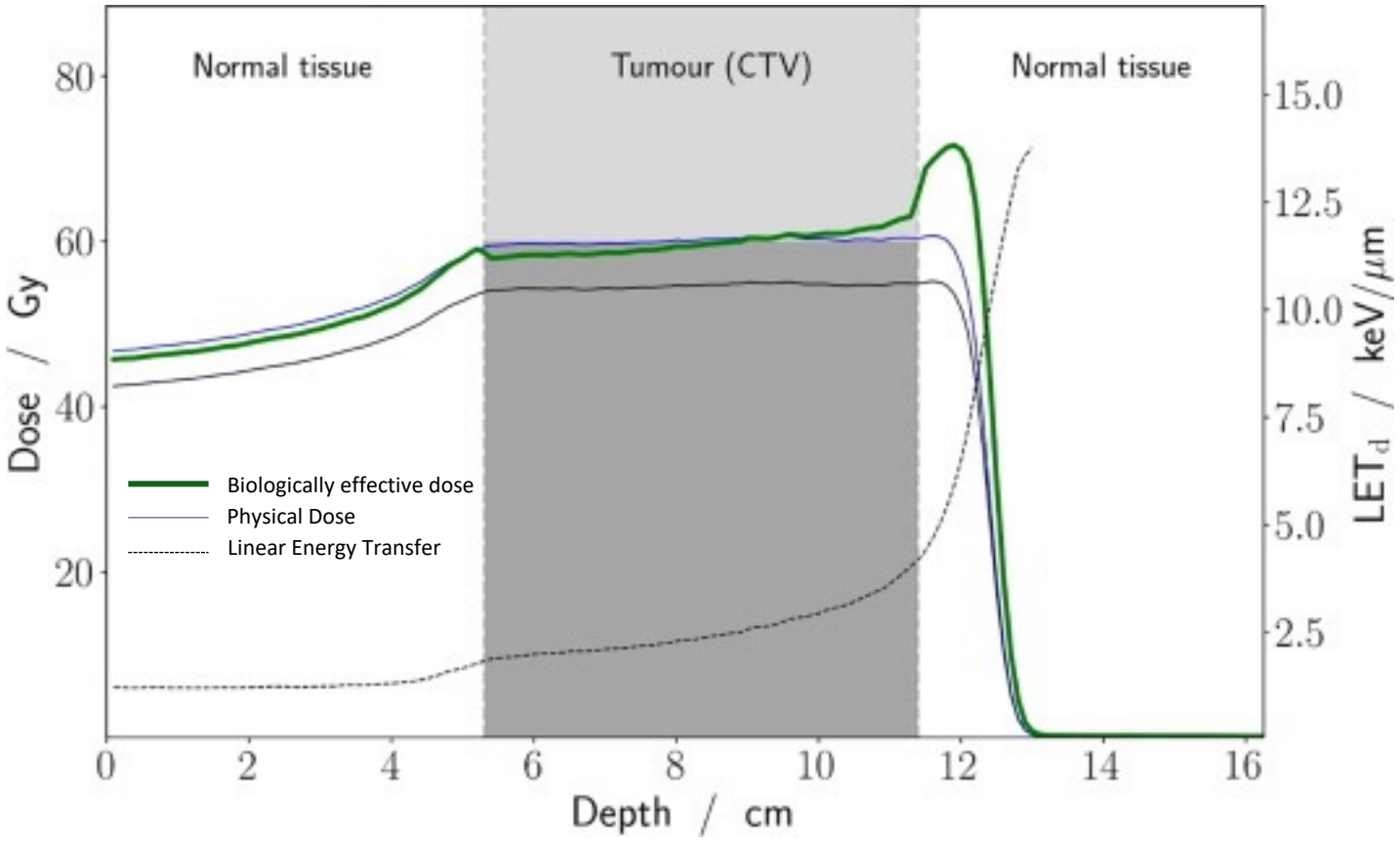
How do we measure biological effect?

What happens in the clinic vs reality



Sørensen BS et al, Radiother. Oncol. (2021)

Relative Biological Effectiveness (RBE)

- RBE measures the biological effectiveness of radiation compared to x-rays

How is it used clinically?

- Clinically it is used to scale the physical dose to an organ or target
- In clinics it is assumed to be constant (1.1) but in reality, it varies with:
  - Linear energy transfer
  - Tissue-specific parameters
  - Dose
  - Dose-rate
- Therefore, when LET increases the RBE and biologically effective dose increases

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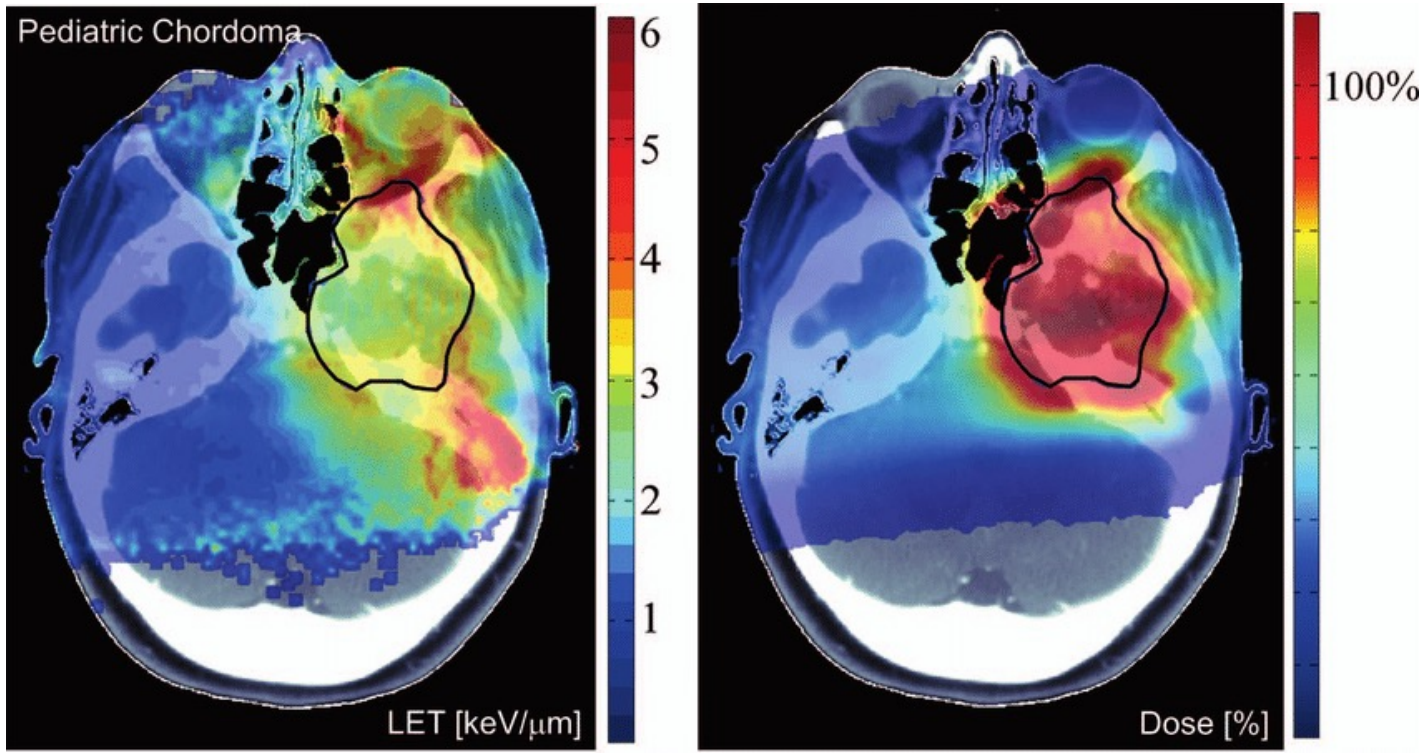
Radiobiological Uncertainty in Proton Therapy



Paganetti H, Int. J. Part. Ther. (2018)

- This increase in LET at the distal end of the Bragg Peak can lead to “invisible” LET hotspots where the biological effect is being underestimated
- These hotspots are often in normal tissue and organs at risk
- There is a shift towards using a variable RBE in treatment plans

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How is RBE derived?

Build survival curve (vs dose) for x-ray and test radiation

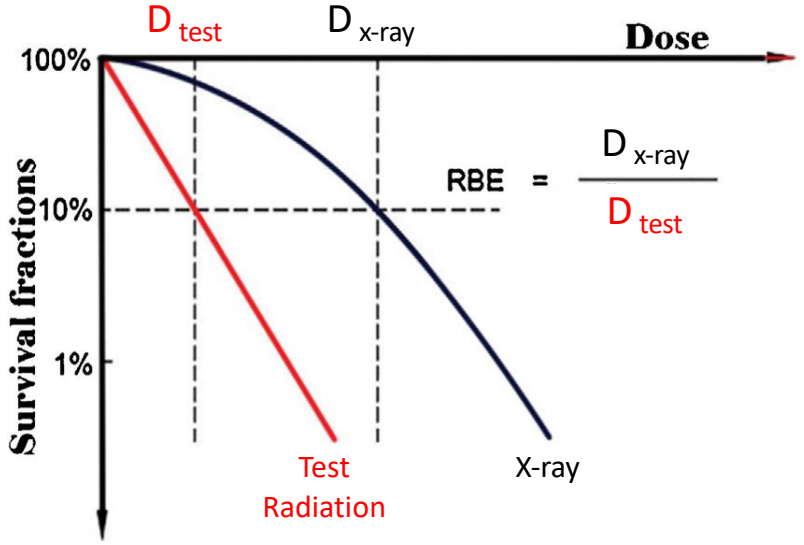
Fit Linear-Quadratic model to each curve $S = \exp(-\alpha D - \beta D^2)$

Parameters α, β quantify response (α/β ratio)

Interpolate the two survival curves at the same survival fraction

Take the ratio of x-ray and test radiation doses to give the same survival

Cell survival experiments



Linear Quadratic (LQ) model

$$S = \exp(-\alpha D - \beta D^2)$$

Where S = survival fraction, D = physical dose, α, β = fit parameters

- Common problems with the LQ model include:
  - Too fewer parameters to accurately describe the system
  - Loses validity at high dose and LET

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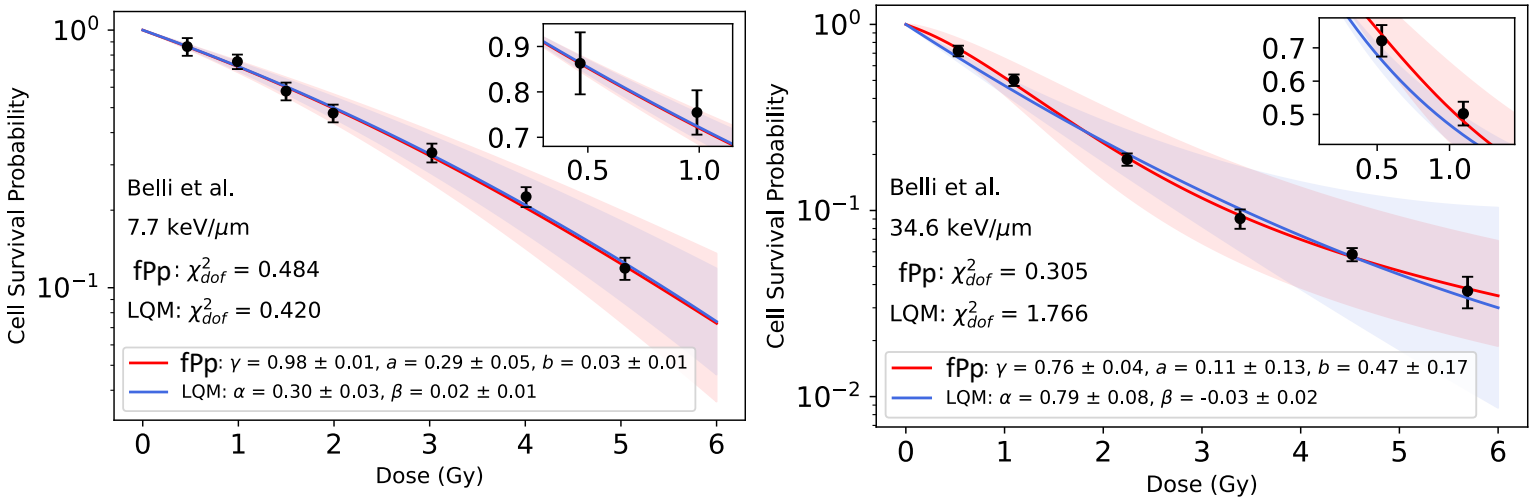
Is there a model that performs better?

Fractional Poisson process (fPp)



- FPp model yields an improved fit for high LET data and a similar fit for low LET proton data (as $\gamma \rightarrow 1$)
- Meaning the LQ model can be expanded to better model high LET cell survival data using a fractional Poisson process

Question: Does using a better fitting model make a difference in the RBE calculation?

Data from Belli M et al, Int. J Rad. Biol. (1998)

Cell Survival Models:

- Linear Quadratic (LQ) model
  - $S = \exp(-\alpha D - \beta D^2)$
- Fractional Poisson Process (fPp) model

$$S = \mathrm{E}_\gamma[-(\alpha D + \beta D^2)^\gamma]$$

where

$$\mathrm{E}_\gamma[-\alpha D - \beta D^2] = \sum_{k=0}^{\infty} \frac{(-\alpha D - \beta D^2)^k}{\Gamma(\gamma k + 1)}$$

- As $\gamma \rightarrow 1$ the LQ and fPp models become equivalent

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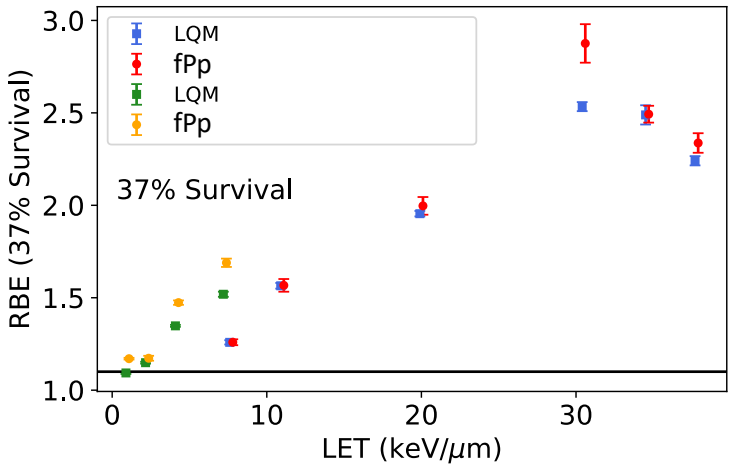
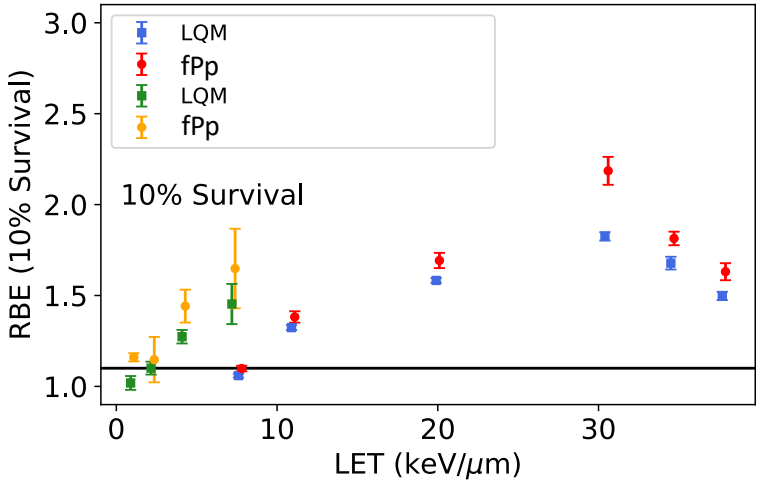
Does using a more accurate model change the RBE prediction?

Low Dose



High Dose



Question: How can we assess model dependence of RBE at the clinical level?

- RBE predictions remain similar between the two models for low dose and low LET data
- A difference arises in the high dose and high LET region (where the LQ model is less accurate)

RBE predicted for data from Belli M et al, Int. J Rad. Biol. (1998)

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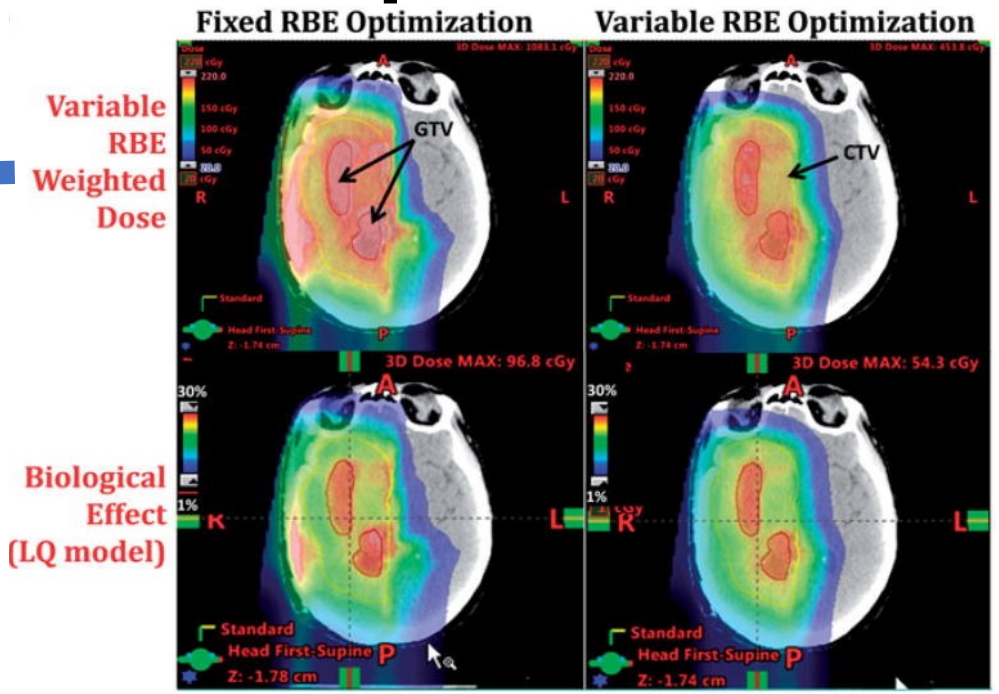
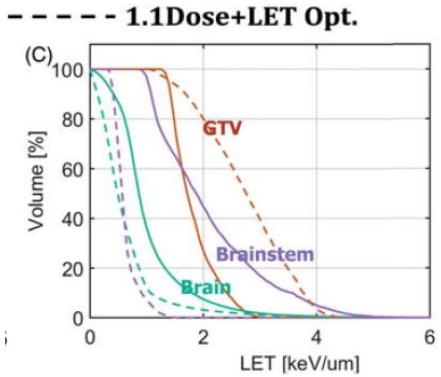
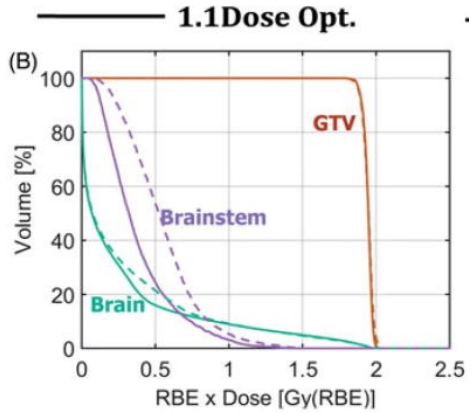
How can this be implemented clinically?

Mohan R, Acta Oncol. (2017)







Compare
Linear-Quadratic Model
Vs
Fractional Poisson Model

- Create a plan using variable and fixed RBE
- Derive dose-volume-histograms (DVH) using D(RBE) for each case
- Make an LET-volume-histogram with LET constraints for each organ
- Use RBE predictions from LQ and fPp model

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Conclusions

- Proton therapy is a precise treatment but comes with uncertainties
- It is important to understand the *cumulative* effect of these uncertainties
  - Including radiobiological uncertainties
- RBE predictions are model dependent
  - Particularly in the high LET region for proton and heavy ion therapy
- There is a way to test whether RBE prediction model dependence is visible at the clinical level

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Future Work

- Further test the fPp model's predictive power for different cell lines under:
  - Different fractionation schedules
  - Different conditions
  - Heavy ion irradiation

- Constrain the parameters of the fPp model:
  - Derive an α/β ratio equivalent expression to compare with LQ Model
  - Determine whether using a more accurate cell survival model for RBE predictions will have a visible effect at the clinical level

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